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FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2016/2017

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A CPRE no tratamento paliativo das obstruções biliares por
patologia maligna: A experiência de um centro

Endoscopic palliation of malignant biliary strictures: A single
center experience

março, 2017

FMUP

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Mestrado Integrado em Medicina

Área: Cirurgia Geral
Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:
Mestre Carlos Alberto Sousa Soares

Trabalho organizado de acordo com as normas da revista:
Portuguese Journal of Gastroenterology

março, 2017

FMUP

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Cirurgia Geral

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

A CPRE no tratamento paliativo das obstruções biliares por patologia maligna: A experiência de um centro

ORIENTADOR

Mestre Carlos Alberto Sousa Soares

COORDINADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTA TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.

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Faculdade de Medicina da Universidade do Porto, 22 / 03 / 2017

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COVER LETTER

We intend to submit our manuscript, an original article, entitled *Endoscopic palliation of malignant biliary strictures: A single center experience*, to the *Portuguese Journal of Gastroenterology*. Our study assessed the outcomes of ERCP guided biliary drainage on the palliative care of patients with malignant biliary obstructions treated at Centro Hospitalar Tâmega e Sousa, E.P.E., and identified patient and tumor related factors with significant impact on patients' survival. We believe our work is relevant for the readership of this journal, since it provides a detailed characterization of hard and surrogate outcomes of an extensively used Gastroenterology technique on a specific population. This manuscript has not been published and is not under consideration for publication in any other journal. All authors approved the manuscript and its submission to this journal, and have no conflicts of interest.

Endoscopic palliation of malignant biliary strictures: A single center experience

A CPRE no tratamento paliativo das obstruções biliares por patologia maligna: A experiência de um centro

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ABSTRACT AND KEYWORDS

Background and Aims: Malignant biliary strictures (MBS) are generally associated with advanced neoplasms at the time of diagnosis and with a poor prognosis. In most cases, the only therapeutic option is palliative care. Endoscopic retrograde cholangiopancreatography (ERCP) guided biliary drainage is the standard of care for these patients. The aim of this study was to evaluate the outcomes of this technique on a population of patients with unresectable or inoperable MBS and to assess the impact of certain factors on patients' survival.

Methods: A retrospective analysis of patients with an unresectable/inoperable MBS who attempted ERCP guided biliary drainage at Centro Hospitalar Tâmega e Sousa from January 1st, 2013 to September 30th, 2016 was performed. The outcomes evaluated included technical success, functional success, early and late complications, stent patency and patient survival. A multivariate analysis was performed to identify the variables associated with survival.

Results: Seventy-seven patients were included in the study. Mean patient age was 76.7 years. The most frequent cause of MBS was pancreatic carcinoma (48.1%), followed by cholangiocarcinoma (31.2%). Technical success of the first ERCP guided biliary drainage was 66.2%. Median total bilirubin relative decrease was 71.1%. Early and late complications rates were 26% and 31.8%, respectively. Median stent patency was 68 days and median patient survival after biliary drainage was 98 days. In multivariate analysis, age at diagnosis, etiology of the stricture, pretreatment total bilirubin and leukocyte levels were significantly associated with survival.

Conclusions: ERCP guided biliary drainage outcomes depend on patient and tumor characteristics, as well as on institutional volume and experience. Patient survival is related to age at diagnosis, etiology of the stricture and pretreatment total bilirubin and leukocyte levels.

Key messages: ERCP guided biliary drainage is the cornerstone of palliative care for most patients with MBS. Patient and tumor characteristics influence patients' prognosis.

Keywords: malignant biliary strictures; palliation; ERCP; biliary drainage.

53 RESUMO E PALAVRAS-CHAVE

54 **Introdução e Objetivos:** As obstruções biliares por patologia maligna (OBPM) estão geralmente
55 associadas a neoplasias avançadas e a um mau prognóstico. A maioria tem indicação para
56 tratamento paliativo, sendo a drenagem biliar por colangiopancreatografia retrógrada
57 endoscópica (CPRE) a abordagem-padrão nestes casos. O objetivo deste estudo foi avaliar os
58 resultados desta técnica em pacientes com OBPM irressecável/inoperável e avaliar o impacto
59 de alguns fatores na sobrevida.

60 **Métodos:** Realizou-se uma análise retrospectiva dos doentes com OBPM irressecável/inoperável
61 submetidos a drenagem biliar por CPRE no Centro Hospitalar Tâmega e Sousa entre 01-01-2013
62 e 30-09-2016. Os resultados avaliados incluíram: sucesso técnico, sucesso funcional,
63 complicações precoces e tardias, patência da prótese e sobrevida. Realizou-se uma análise
64 multivariada para identificar as variáveis com impacto na sobrevida dos doentes.

65 **Resultados:** Foram incluídos neste estudo 77 doentes com uma idade média de 76,7 anos. A
66 causa mais frequente de OBPM foi o carcinoma pancreático (48,1%), seguido do
67 colangiocarcinoma (31,2%). O sucesso técnico do primeiro procedimento foi de 66,2%. A
68 mediana da diminuição da bilirrubina total foi de 71,1%. As taxas de complicações precoces e
69 tardias foram de 26% e 31,8%, respetivamente. As medianas da patência da prótese e da
70 sobrevida após a drenagem biliar foram de 68 e 98 dias, respetivamente. Na análise
71 multivariada, a idade, a etiologia da obstrução e os níveis pré-tratamento de bilirrubina total e
72 de leucócitos associaram-se significativamente com a sobrevida.

73 **Conclusões:** Os resultados da drenagem biliar por CPRE estão relacionados com as
74 características do doente e do tumor, bem como com o volume e a experiência da instituição. A
75 sobrevida dos doentes depende da idade, da etiologia da OBPM e dos níveis pré-tratamento de
76 bilirrubina total e de leucócitos.

77 **Mensagens-chave:** A drenagem biliar por CPRE é um fulcral no tratamento paliativo das OBPM.
78 As características do doente e do tumor influenciam o prognóstico.

- 79 **Palavras-chave:** obstruções biliares por patologia maligna; tratamento paliativo; CPRE;
- 80 drenagem biliar.

INTRODUCTION

Malignant biliary strictures (MBS) are rare, but their incidence seems to be increasing with time and they are generally associated with a poor prognosis [1-3]. They are caused by a variety of neoplasms and can occur as the initial manifestation of the disease or appear with its progression [1]. The most common causes of MBS are pancreatic carcinomas and cholangiocarcinomas [1, 2, 4]. Less frequent causes of MBS include ampullary carcinomas, duodenal primary carcinomas, neuroendocrine pancreatic tumors, gallbladder carcinomas, primary or secondary liver neoplasms and hilar obstructions by *porta hepatis* adenopathies secondary to locoregional metastases or lymphomas [1, 2, 4]. Biliary obstructions occur in 70-90% of patients with neoplasms involving the biliary tree [2] and 75% of cephalopancreatic ductal adenocarcinomas manifest with jaundice [5].

MBS are classified, according to their location, in intra- and extra-hepatic [6, 7]. Intra-hepatic focal malignant obstructions are rare and frequently found incidentally [7]. Since most of these cases do not have indication for biliary drainage, they will not be included in this study.

Extra-hepatic (hilar or distal) strictures are the most common causes of MBS [7], and usually manifest with nonspecific symptoms, like jaundice, pruritus, anorexia and malaise, which can also be present in benign conditions [1, 2]. Cholestasis is associated with debilitating symptoms and can interfere with cellular immunity and cause immunosuppression, facilitating tumor growth and metastatic spread [1, 5]. It also predisposes patients to infection, systemic inflammatory response syndrome and sepsis [1, 5]. Furthermore, cholestasis reduces the bile flow to the enteric system, impairing fat soluble vitamins absorption and predisposing the patient to the associated complications [1].

Hilar MBS are less frequent than the distal causes, and include cholangiocarcinomas and neoplasms involving the hepatic confluence by direct extension from the gallbladder, liver or metastatic nodal disease [4, 6].

Contrast enhanced computed tomography (CT) and/or magnetic resonance cholangiopancreatography (MRCP) are necessary for diagnosis, adequate assessment of tumor relations to the biliary and vascular anatomy and for treatment planning [4]. The role of pathological analysis on determining the etiology of the obstruction is limited by its low sensitivity [8, 9].

The poor prognosis associated with MBS is secondary to the locoregional invasiveness of these neoplasms, high rate of distant metastases, late symptomatology onset and higher incidence in the elderly, which makes them frequently unresectable and/or inoperable at the time of diagnosis [3, 8]. Although in certain cases downstaging is possible, with neoadjuvant chemo- and/or radiotherapy, making some tumors resectable, in most cases the only therapeutic option is palliative care [1, 3].

Biliary drainage is the cornerstone of treatment of such obstructions, as it provides symptomatic relief and quality of life improvements, avoids some of the complications associated with cholestasis and jaundice, prolongs survival, and, in some cases, enables “bridging” to curative surgical treatment [1, 10-12]. Biliary drainage can be achieved by three distinct approaches: bilioenteric anastomosis (a General Surgery procedure), percutaneous biliary drainage (an Interventional Radiology procedure) and endoscopic biliary drainage (by endoscopic retrograde cholangiopancreatography (ERCP) or, more recently, by endoscopic ultrasound, both Gastroenterology procedures) [2, 13].

In the past, biliary drainage was confined to surgical bypass, but recently minimally invasive techniques have assumed an increasingly important role [4, 12]. Surgical bypass, when feasible, is associated with low recurrent jaundice rates (2-5%) but with higher morbi-mortality rates compared to minimally invasive techniques, and is more expensive [2, 4, 14]. ERCP guided biliary drainage is the standard of care and is preferred to percutaneous biliary drainage for most extra-hepatic malignant strictures, since it is less invasive and provides similar results [1, 11]. For hilar lesions, namely type II-IV hilar MBS, percutaneous biliary drainage seems to provide a

higher success rate and less infectious complications [1, 11]. Furthermore, minimally invasive biliary drainage procedures allow evaluation of the biliary tree anatomy and tissue sample collection for pathological analysis [15].

ERCP stents are in constant technological evolution and may be divided into two major categories: plastic stents (PS) and self-expandable metallic stents (SEMS) [1-4, 6]. The selection between these two types of stents depends on diagnostic certainty, expected survival and cost-efficacy relation, and must be personalized according to the characteristics of each patient [1, 16, 17].

The aim of our retrospective analysis was to evaluate ERCP guided biliary drainage outcomes, namely technical and functional success rates, early and late complications, stent patency and survival on patients with unresectable or inoperable MBS admitted to Centro Hospitalar Tâmega e Sousa (CHTS) between January 1st, 2013 and September 30th, 2016. Additionally, we evaluated the impact of certain demographic, clinical, biochemical and treatment-related factors on patient survival.

MATERIALS AND METHODS

A retrospective analysis of a prospective cohort of all consecutive patients with an unresectable or inoperable MBS that attempted palliative ERCP guided biliary drainage at CHTS from January 1st, 2013 to September 30th, 2016 was performed. The study was approved by the Hospital's Ethical Committee and Administration Board.

All patients, 18 years or older, with the diagnosis of a MBS with indication for palliative biliary drainage (based on disease extent or patients' medical fitness), having undergone the first ERCP guided biliary drainage attempt from January 1st, 2013 to September 30th, 2016 at CHTS were included in the study. Patients undergoing ERCP with stent placement as a "bridging" technique for a future therapy with a potentially curative intent and patients undergoing biliary drainage by other techniques, namely surgical, percutaneous or endoscopic ultrasonography guided, were excluded from the study.

Diagnosis was based on clinical, laboratory and imaging results (ultrasonography, CT, MRCP and/or ERCP) and, when possible, pathological analysis of a biopsy or exfoliative cytology specimen.

ERCP was performed by one of the authors, an experienced endoscopist, using a therapeutic duodenoscope. During the procedure, patients were under sedation, monitored and supervised by an anesthesiologist, in the prone position. After performing a cholangiogram, a guidewire was passed through the stricture and a biliary stent was placed using a delivery system. Both PS and SEMS were used. Sphincterotomy was performed when necessary to facilitate more complex stenting procedures.

Data was collected from the ERCP hospital registry and from the patients' medical records from January 1st, 2013 until the patients' death or until the end of the follow-up period (November 30th, 2016). Patients' demographic information and American Society of Anesthesiologists (ASA) physical status classification were registered. Dates of malignancy diagnosis, biliary drainage and death were recorded. Imaging techniques results, pathological

reports, ERCP reports, hospital notes and blood laboratory analysis, before and after stent placement, were reviewed.

The first ERCP with therapeutic intent performed in each patient was evaluated. If it failed to correctly place a stent and the procedure was later repeated, we also collected data from subsequent ERCP procedures (until effective stent placement), in order to evaluate the global efficacy of ERCP in this context.

A descriptive statistical characterization of the studied population was performed. The biliary drainage outcomes assessed were: technical success (successful stent placement through the stricture and flow of bile or contrast medium through the stent), functional success (decrease in total bilirubin levels), early (≤ 30 days) and late (> 30 days) complications rates, median overall stent patency (time between successful biliary drainage and stent occlusion, stent prophylactic substitution, patients' death or end of follow-up period) and median stent patency until occlusion, and median survival (time between successful biliary drainage and patients' death or end of follow-up period). Thirty-day mortality rate was calculated. Overall survival was evaluated and registered using a Kaplan-Meier curve. A multivariate analysis using Cox regression was performed in order to identify factors influencing patients' survival. The studied variables included: age at diagnosis, sex, ASA classification, established diagnosis, pretreatment blood analysis levels (total bilirubin, hemoglobin, leukocytes, C-reactive protein (CRP), serum albumin, International Normalized Ratio (INR) and serum creatinine levels) and chemotherapy. A p -value of < 0.05 was considered significant and 95% confidence intervals were used. The statistical analysis was performed using Stata (version 14.0 for MacOS) and SPSS (version 24.0 for MacOS).

RESULTS

Seventy-seven patients were considered eligible for the study, and follow-up data until death or until the end of the data collection period (November 30th, 2016) was obtained for all. The characteristics of the study population are presented in Table 1. Mean age at diagnosis was 76.7 years and 51.9% of the patients were male.

The most frequent cause of MBS was pancreatic carcinoma (48.1% of patients), followed by cholangiocarcinoma (31.2%). It was not possible to determine the origin of the malignancy in 3 patients (3.9%). Pathological diagnostic confirmation was obtained in only 20 patients (26%).

During the period between January 1st, 2013 and September 30th, 2016 (45 months) 83 ERCPs for MBS were performed. PS were used in 50 patients (89.3%) and SEMS in 6 (10.7%). 59 patients (76.6%) underwent sphincterotomy to facilitate the biliary tree cannulation.

Table 2 displays the ERCP guided biliary drainage outcomes. The first ERCP guided biliary drainage was technically successful in 51 of the 77 patients (66.2%). A second attempt was performed in 6 patients with technical success in 5 (83.3%).

Functional success was evaluated by the decrease in total bilirubin levels. Median pretreatment total bilirubin level was 17.9mg/dL and median post treatment total bilirubin level was 4.2mg/dL. The median absolute decrease was 11.3mg/dL and the median decrease rate was 71.1%.

Early complications occurred in 20 patients (26%) and included cholangitis (90%), pancreatitis (5%) and stent dysfunction (5%). Late complications occurred in 14 patients (31.8%) and included stent dysfunction (57.1%) and cholangitis (42.9%).

Stents were functional at the end of the data collection period in 7 of the 56 patients in whom biliary drainage was technically successful (median follow-up time: 447 days). Planned stent substitution was performed in the absence of stent dysfunction in 6 patients (12.2%), occlusion occurred in 10 patients (20.4%) and 33 patients (67.3%) died before stent dysfunction or substitution.

Median overall stent patency was 68 days and median patency until occlusion was 57.5 days. Kaplan-Meier cumulative patency analysis was performed (Figure 1). Patency cumulative rates were 71.4%, 40.4%, 23.1% and 9.2% at 1, 3, 6 and 12 months, respectively.

There were no immediate deaths associated with the procedure. Thirty-day mortality rate after the first ERCP was 20.8%. At the end of the follow-up period only 7 patients (9.1%) were alive. A Kaplan-Meier cumulative survival analysis was performed, as shown in Figure 2. Median survival time after successful biliary drainage was 98 days. The curve shows that the survival rates after the first ERCP were 76.8%, 51.3%, 25.7% and 11.5% at 1, 3, 6 and 12 months, respectively.

Multivariate analysis (Table 3) identified older age at diagnosis (Hazard Ratio (HR)=1.11, $p=0.009$), diagnosis of hepatic metastasis from non-hepatobiliopancreatic (HBP) primary neoplasms (HR=50.68, $p=0.007$), high pretreatment total bilirubin levels (HR=1.07, $p=0.014$) and high pretreatment leukocyte levels (HR=1.29, $p=0.028$) as negative predictors of survival.

DISCUSSION AND CONCLUSIONS

Seventy-seven patients were included in the study and 40 of them were males (51.9%), which is similar to the results published by other studies [5, 18, 19]. On the other hand, the mean age of our population was 76.7 years, higher than that reported in other studies [12, 18-21], which may have had a negative effect on some outcomes evaluated in our study, namely survival. It also highlights the importance of palliative care of patients with MBS: elderly patients may be unfit for surgery and other aggressive approaches (even in the presence of resectable tumors) given their frailty, and a palliative approach may be the only viable therapeutic option in order to improve the patients' quality of life. However, even though most patients were elderly, some were as young as 51 years of age. This reflects the aggressiveness of some of the underlying malignancies and the paucity of clinical signs and symptoms that could allow an early diagnosis, impeding a curative intent even in young patients.

Patients ASA status was included as an indicator of their physical status. 46.2% of patients were classified as ASA-2 (mild to moderate systemic disease without functional impairment) and 47.7% as ASA-3 (severe systemic disease with functional impairment). Therefore, even though ASA status did not influence survival on multivariate analysis, certain characteristics of the studied population, namely comorbidities and poor underlying physical condition, might have had a deleterious effect on biliary drainage outcomes and prognosis.

The most common etiology of MBS was pancreatic carcinoma (48.1% of cases), followed by cholangiocarcinoma (31.2% of cases). Rarer causes included ampullary carcinoma, gallbladder carcinoma and hepatic metastasis from non-HBP primary neoplasms, resembling the frequencies reported by other authors [12, 19, 21]. Pathological diagnostic confirmation was obtained in 26% of patients; in the remainder, diagnosis was based on clinical, imaging and laboratory results. Similar pathological confirmation rates have been reported by other authors, reflecting the importance of imaging techniques on establishing diagnosis and treatment algorithms nowadays [18, 19]. Despite having a limited sensitivity and also the possibility of

associated morbidity due to the attempts to obtain the specimens, pathological analysis plays an important role on prognosis determination and treatment planning in some patients [8, 9], and endoscopists should be encouraged to collect tissue samples whenever possible. Combining biopsy and exfoliative cytology or performing multiple sample collections by one of these methods increases the sensitivity of the procedure [9]. New pathological techniques are currently being developed in order to improve analysis sensitivity and specificity [9].

Our results revealed an ERCP guided biliary drainage technical success rate of 66.2% on the first ERCP and of 83.3% on the second attempt, whenever the first failed. Some studies report higher technical success rates on the first ERCP, but similar rates on the second procedure [1, 11-13, 17]. According to the literature, the technique can fail for several reasons, such as difficulties on reaching the papilla, on cannulating the bile ducts or on retrogradely passing the stenosis, and success rate is influenced by the endoscopist's experience, volume of procedures performed in the center, adequate patient sedation and type of neoplasms included in the study, and is not influenced by the type of stent used [11, 22]. In our institution, more than 200 ERCPs are performed annually by a single endoscopist. The lower technical success rate found in our study may be related to endoscopist's experience or institutional volume but also to the advanced stage of some malignancies, therefore impeding the passage of the duodenoscope through the duodenum, the papilla or the stricture, and to the heterogeneity of neoplasms assessed, including hilar cholangiocarcinomas and hepatic metastasis from non-HBP primary neoplasms, with an associated increase in the technical difficulty of the procedure.

Median pretreatment total bilirubin level was 17.9mg/dL, and patients with a technically successful ERCP had a median decrease in total bilirubin level of 11.3mg/dL. 43 patients (76.8%) had a total bilirubin decrease rate superior to 20%, a similar proportion to that obtained by Abraham and colleagues (78%) [21]. The median decrease rate observed in this series was 71.1%, indicating that most patients have a significant improvement in cholestasis after the procedure. We also evaluated the percentage of patients with normalization of the total

285 bilirubin level (post-treatment bilirubin levels $\leq 2\text{mg/dL}$), and verified that it only occurred in 12
286 patients (21.4%). Weston and colleagues reported a much higher normalization rate (76%) [23].
287 However, it must be considered that the post-treatment total bilirubin level was obtained by
288 retrospectively reviewing patients blood analysis results available on their medical records
289 (either performed while the patient was still admitted to the hospital or after discharge) and
290 that it may not reflect the lowest total bilirubin level reached over the post-treatment period,
291 as would be ideal. According to the available literature, some patient and tumor related factors
292 seem to decrease the likelihood of functional success, namely high pretreatment bilirubin levels,
293 $\text{INR} \geq 1.5$ and the presence of diffuse liver metastases [11].

294 In this series, post-ERCP early complications occurred in 26% of patients. The most
295 frequent early complication was cholangitis, as was expected from the literature review [11, 12,
296 18, 24]. At our institution, ESGE guidelines are followed, and antibiotic prophylaxis is only
297 administered to high risk patients or if incomplete biliary drainage is anticipated [11]. However,
298 broad-spectrum antibiotics are prophylactically administered to all patients in some centers,
299 which might be responsible for the lower complication rates reported in those centers (5-10%),
300 with a significantly lower incidence of infection [18, 24].

301 Late complications occurred in 31.8% of patients, and were more frequently observed in
302 patients with PS (32.5% vs 25.0%), as expected. The most common late complication was stent
303 dysfunction, followed by cholangitis, as reported by others [11]. Our overall late morbidity rate
304 reflects the PS morbidity rate, since it was used in 89.3% of patients. The difference in late
305 complications rates between the two stent types is in accordance with that reported in the
306 literature [1-4, 11, 12, 17, 18].

307 Median overall stent patency was 68 days (2.3 months). This variable included patients
308 who had their stents prophylactically substituted, who died before stent dysfunction and who
309 had the stent still patent at the end of the follow-up period. It is important to remember that PS
310 were used in most patients, and that this type of stent is associated with a shorter stent patency

than SEMS, as indicated in a meta-analysis performed by Moss and colleagues: median PS patency varied from 2 to 5.5 months and median SEMS patency from 3.7 to 9.1 months [25].

Median patient survival in our study population, from the first successful biliary drainage, was 98 days (3.3 months), which is less than that reported in the literature (4-7.4 months) [12, 19]. The shorter survival reported in our series may be related to a relatively older population group with a poorer physical status in comparison to other similar studies, to the exclusion of patients with possible indication for a curative intent treatment and to the inclusion of malignancies with an overall worse prognosis.

In multivariate analysis, four factors were identified as independent negative predictors of survival: older age at diagnosis, diagnosis of hepatic metastases from non-HBP primary neoplasms, high pretreatment total bilirubin levels and high pretreatment blood leukocyte levels. Older age at diagnosis, as previously discussed, is frequently associated with a poorer functional status, the probable reason for the shortened survival. This correlation has also been reported by others [5, 26]. Controversially, Weaver and colleagues indicated that an older age at diagnosis was associated with a prolonged survival, stating that it was possibly because older people tend to have less aggressive tumors [19]. Such association, to the best of our knowledge, has not been reported elsewhere. Regarding the etiology of the stricture, our analysis showed that hepatic metastases from non-HBP primary neoplasms were associated with a poor prognosis, probably because they reflect an advanced stage of a neoplasm unresponsive to systemic therapy. Similarly to our findings, hyperbilirubinemia has been reported in the literature to be negatively associated with survival, probably because cholestasis facilitates tumor growth and metastatic spread and predisposes patients to a variety of complications [5, 27]. As suggested by our study, high blood leukocyte levels seem to be an independent predictor of shorter survival, especially in patients with pancreatic carcinomas [28]. Some authors have described a correlation between the intensity of the systemic inflammatory response and the aggressiveness of such neoplasms [29]. Several studies have identified a variety of other factors

significantly affecting survival. Some of these covariates were included in our study but were not found to be significant predictors of survival (hemoglobin, serum albumin and chemotherapy), and others were not assessed (clinical stage) [12, 28]. The identification of survival predictors is very important for prognosis assessment and treatment planning. However, because study designs and population characteristics are widely variable between studies, there is no consensus on what factors should be used for prognosis determination.

Our investigation presents some limitations. We studied a small heterogeneous population group assisted at a single institution, which reduces the probability of finding statistically significant results and affects the generalizability of the study. The fact that we included patients older than those enrolled in most of the studies published in the literature may help to fill a blank space in the prognostic evaluation of the more elderly. In a retrospective study, like ours, misclassification bias is more likely to occur and data may not be available for analysis. A careful and organized data collection was performed to minimize these possible error sources. Selection bias may also have occurred: patients with an initial indication for a potentially curative treatment attempt were excluded from the study even if their disease was considered “borderline resectable” on admission; some of these patients may have been later considered not resectable. This would make them eligible for our study, possibly changing the baseline characteristics of our population (like age and comorbidities), as well as some of the outcomes assessed, namely overall survival.

Few studies have focused on palliative biliary drainage, and to our knowledge only one comparable study has been developed in Portugal, which focused on hilar cholangiocarcinomas and not on all MBS [18]. Therefore, we consider our study to be of great utility, locally and in other centers, not only because it reinforces the usefulness of ERCP guided biliary drainage on the palliative care of MBS, but also because it encourages the development of early diagnosis approaches and of new algorithms for prognosis prediction, therefore ensuring a more individualized and cost-effective approach. It also stimulates the development of a prospective

multicentric study on ERCP guided biliary drainage. This study design would guarantee better study conditions with a closer follow-up and a more accurate assessment of patient and tumor characteristics and of primary and secondary outcomes.

Another challenge for the near future is the development of techniques that provide a sustained symptomatic relief. Endoscopic procedures currently under investigation and showing promising results include intraductal radiofrequency ablation, photodynamic therapeutics and intratumoral injection of chemotherapeutic and immunologic agents [5, 6]. These techniques will probably play an increasingly important role on the palliation of MBS.

371 **STATEMENT OF ETHICS**

372 The study was approved by the Hospital's Ethical Committee and Administration Board.

AUTHOR CONTRIBUTIONS

All authors played an important role on study conception/design, data collection, analysis or interpretation, and manuscript writing or revision. Margarida Mendes and Carlos Soares, the main investigators, were responsible for all stages of the study. Cláudia Dias and Joana Mendes contributed with data analysis and interpretation and manuscript revision. Jorge Silva, the endoscopist who performed the ERCP guided biliary drainage procedures, helped with data collection and manuscript revision. João Pinto-de-Sousa contributed with study design, data analysis and manuscript revision. The submitted version of the manuscript has been approved by all.

382 **CONFLICTS OF INTEREST**

383 The authors declare no conflicts of interest.

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TABLES AND FIGURES LEGENDS

Table 1 – *Characteristics of the studied population.*

SD – standard deviation; ASA – American Society of Anesthesiologists; IQR – Interquartile range; CRP – C-Reactive Protein; INR – International Normalized Ratio.

Table 2 - *ERCP guided biliary drainage outcomes.*

ERCP – endoscopic retrograde cholangiopancreatography; IQR – Interquartile range; CI – confidence interval.

Table 3 - *Multivariate analysis of possible predictors of survival.*

HR – Hazard Ratio; CI – Confidence Interval; ASA – American Society of Anesthesiologists; HBP – hepatobiliopancreatic; INR – International Normalized Ratio; CRP – C-Reactive Protein.

Figure 1 - Kaplan-Meier cumulative stent patency curve showing stent patency after successful ERCP guided biliary drainage in patients with unresectable/inoperable malignant biliary strictures treated at CHTS from January 1st, 2013 to September 30th, 2016.

Figure 2 - Kaplan-Meier cumulative survival curve showing patients' survival after successful ERCP guided biliary drainage in patients with unresectable/inoperable malignant biliary strictures treated at CHTS from January 1st, 2013 to September 30th, 2016.

TABLES

Table 1 – Characteristics of the studied population	
<i>Age at diagnosis (years)</i>	
Mean (SD)	76.7 (9.6)
Range	51-94
<i>Sex (n (%))</i>	
Male	40 (51.9)
Female	37 (48.1)
<i>ASA classification (n (%))</i>	
1	0 (0)
2	30 (46.2)
3	31 (47.7)
4	4 (6.2)
<i>Diagnosis (n (%))</i>	
Pancreatic carcinoma	37 (48.1)
Cholangiocarcinoma	24 (31.2)
Ampullary carcinoma	7 (9.1)
Gallbladder carcinoma	1 (1.3)
Hepatic metastasis	5 (6.5)
Indeterminate malignant obstruction	3 (3.9)
<i>Anatomopathological confirmation (n (%))</i>	
Yes	20 (26.0)
No	57 (74.0)
<i>Pretreatment blood indices</i>	
<i>Total bilirubin levels (mg/dL)</i>	
Median (IQR)	17.9 (12.3-23.8)
<i>Hemoglobin levels (g/dL)</i>	
Median (IQR)	11.3 (10.2-12.6)
<i>Leukocyte levels (10³/μL)</i>	
Median (IQR)	7.65 (6.15-9.58)
<i>CRP levels (mg/L)</i>	
Median (IQR)	32.8 (18.1-74.9)
<i>Albumin levels (g/dL)</i>	
Median (IQR)	2.7 (2.2-3.2)
<i>INR levels</i>	
Median (IQR)	1.07 (0.98-1.15)
<i>Creatinine levels (mg/dL)</i>	
Median (IQR)	0.9 (0.7-1.2)
<i>Chemotherapy (n (%))</i>	
Yes	6 (7.8)
No	71 (92.2)

SD – standard deviation; ASA – American Society of Anesthesiologists; IQR – Interquartile range; CRP – C-Reactive Protein; INR – International Normalized Ratio.

Table 2 – ERCP guided biliary drainage outcomes	
<i>Technical success rate (n (%))</i>	
First ERCP	51 (66.2)
Second ERCP (if first ERCP failed)	5 (83.3)
<i>Functional success</i>	
<i>Post-treatment total bilirubin levels (mg/dL)</i>	
Median (IQR)	4.2 (2.3-9.0)
<i>Decrease in total bilirubin levels (mg/dL)</i>	
Median (IQR)	11.3 (4.5-17.0)
<i>Total bilirubin decrease rate (%)</i>	
Median (IQR)	71.1 (40.3-86.7)
<i>Normalization of total bilirubin levels (≤ 2mg/dL) (n (%))</i>	
Yes	12 (21.4)
No	44 (78.6)
<i>Total bilirubin decrease rate >20% (n (%))</i>	
Yes	43 (76,8)
No	13 (23,2)
<i>Complications</i>	
<i>Early complications (n (%))</i>	
Overall incidence	20 (26)
Cholangitis	18 (90)
Pancreatitis	1 (5)
Stent dysfunction	1 (5)
<i>Late complications (n (%))</i>	
Overall incidence	14 (31.8)
Stent dysfunction	8 (57.1)
Cholangitis	6 (42.9)
By stent type	
Plastic stents	13 (32.5)
Self-expandable metallic stents	1 (25)
<i>Stent patency</i>	
<i>End of Patency (n (%))</i>	
Occlusion	10 (17.9)
Planned substitution	6 (10.7)
Death	33 (58.9)
End of follow-up time	7 (12.5)
<i>Overall patency time (days)</i>	
Median (95% CI)	68.0 (45.6-90.4)
<i>Patency time until occlusion (days)</i>	
Median (IQR)	57.5 (11.5-135.3)
<i>Survival</i>	
Median survival (95% CI) (days)	98.0 (60.5-135.5)
Procedure-associated mortality (n (%))	0 (0)
30-day mortality (n (%))	13 (23.2)

ERCP – endoscopic retrograde cholangiopancreatography; IQR – Interquartile range; CI – confidence interval.

Table 3 – Multivariate analysis of possible predictors of survival			
Variables	HR	95% CI	p-value
<i>Age at diagnosis</i>	1.11	1.03-1.20	0.009
<i>Gender (female vs male)</i>	1.38	0.46-4.13	0.561
<i>ASA Classification</i>			0.216
ASA-2	Ref		
ASA-3	2.26	0.79-6.52	0.131
ASA-4	0.65	0.14-3.02	0.582
<i>Diagnosis</i>			0.039
Pancreatic carcinoma	Ref		
Cholangiocarcinoma	0.77	0.31-1.92	0.571
Hepatic metastasis from non-HBP primary neoplasms	50.68	2.87-895.86	0.007
Ampullary carcinoma	1.24	0.26-5.93	0.790
Unknown	1.20	0.28-5.12	0.801
<i>Pretreatment total bilirubin</i>	1.07	1.01-1.13	0.014
<i>Pretreatment serum albumin</i>	1.63	0.67-3.98	0.281
<i>Pretreatment hemoglobin</i>	1.10	0.84-1.44	0.484
<i>Pretreatment INR</i>	6.12	0.20-185.81	0.297
<i>Pretreatment blood leukocyte</i>	1.29	1.03-1.62	0.028
<i>Pretreatment CRP</i>	0.99	0.97-1.01	0.314
<i>Pretreatment serum creatinine</i>	1.77	0.74-4.21	0.197
<i>Chemotherapy (no vs yes)</i>	0.70	0.09-5.40	0.729

HR – Hazard Ratio; CI – Confidence Interval; ASA – American Society of Anesthesiologists; HBP – hepatobiliopancreatic; INR – International Normalized Ratio; CRP – C-Reactive Protein.

FIGURES

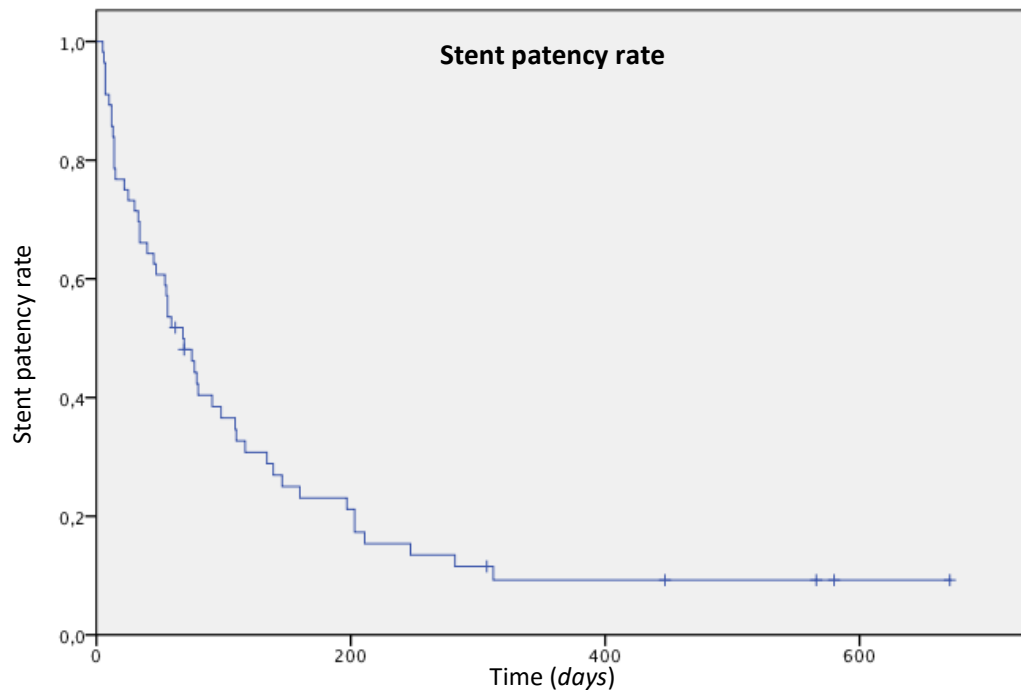


Figure 1 – Kaplan-Meier cumulative stent patency curve showing stent patency after successful ERCP guided biliary drainage in patients with unresectable/inoperable malignant biliary strictures treated at CHTS from January 1st, 2013 to September 30th, 2016.

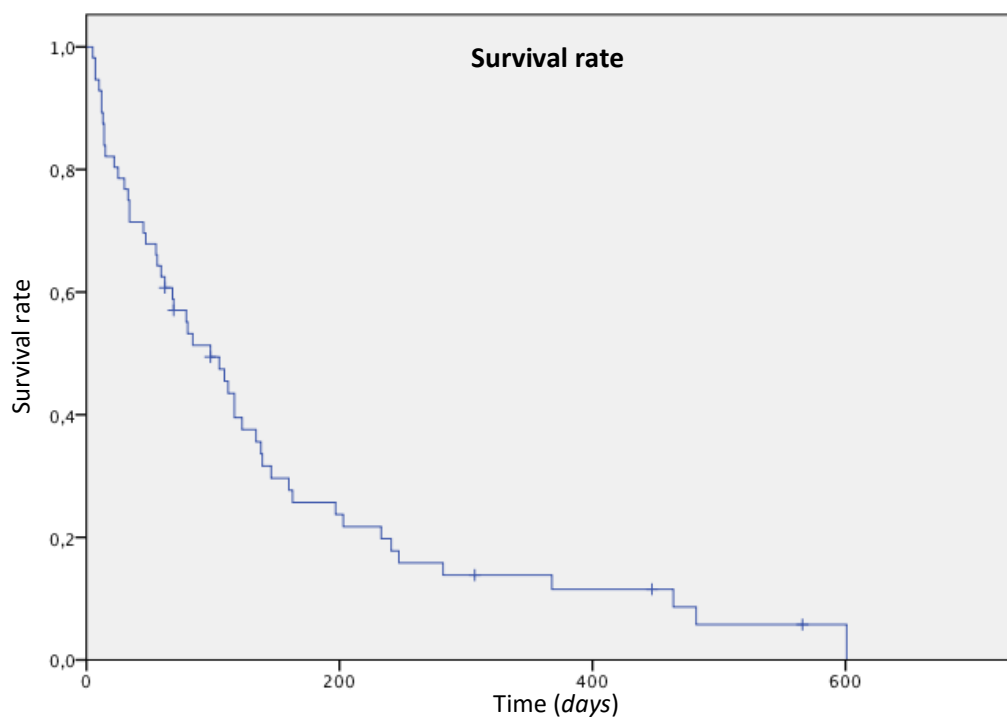


Figure 2 – Kaplan-Meier cumulative survival curve showing patients' survival after successful ERCP guided biliary drainage in patients with unresectable/inoperable malignant biliary strictures treated at CHTS from January 1st, 2013 to September 30th, 2016.

AGRADECIMENTOS

Ao meu orientador, Mestre Carlos Soares, pela disponibilidade, pelo conhecimento transmitido e pelas críticas essenciais à realização deste trabalho.

Ao Prof. Doutor João Pinto-de-Sousa, por me ter acolhido da melhor forma no serviço de Cirurgia Geral e pela disponibilidade para ajudar ao longo de todo o processo de investigação.

À Doutora Cláudia Dias, pela ajuda essencial na elaboração da análise estatística e na interpretação dos resultados obtidos.

Ao Dr. Jorge Silva, por me ter disponibilizado muitos dos dados indispensáveis à realização desta dissertação e pela colaboração ao longo de toda a sua realização.

A todos os meus professores, pelos ensinamentos e pelo exemplo, e à Faculdade de Medicina da Universidade do Porto, pela oportunidade de aprendizagem.

Aos meus pais, pela tranquilidade transmitida, pela confiança que depositam em mim e por me acompanharem em mais um momento importante do meu percurso.

À minha irmã Joana, pela ajuda na elaboração da análise estatística e na revisão do trabalho, pela paciência para as minhas inseguranças e por me ajudar a encontrar sempre as melhores soluções.

Ao meu irmão João, pela calma, por nunca duvidar das minhas capacidades e pela constante disponibilidade para ajudar.

Aos meus avós, aos meus padrinhos e à minha restante família, pela confiança e apoio incondicionais.

À Ana Helena, pelas correções sugeridas, pela disponibilidade para ajudar e por ser uma amiga sempre presente e paciente.

Aos meus restantes amigos, pela compreensão, por me ouvirem sempre e por me acompanharem nos bons e maus momentos.

Anexos

- 1 – Parecer da Comissão de Ética para a Saúde e do Conselho de Administração do Centro Hospitalar Tâmega e Sousa
- 2 – Normas de publicação da revista *Portuguese Journal of Gastroenterology*

Exma. Senhora
Margarida Sofia Soares Mendes
Rua da Cavada Velha, nº83, Branca
Albergaria-a-Velha
margarida_mendes900@hotmail.com

SUA REFERÊNCIA	SUA COMUNICAÇÃO DE	NOSSA REFERÊNCIA	DATA
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ASSUNTO: Pedido de Pesquisa Clínica/Investigação

Acusamos a recepção do seu pedido para realização de Investigação clínica: “ **A CPRE no tratamento paliativo das obstruções biliares por patologia maligna**”.

Agradecemos a preferência pela nossa instituição.

A comissão Ética para a Saúde, não tem objecção ética à sua realização da sua investigação no CHTS.

Estaremos ao dispor para qualquer informação ou esclarecimento que entenda solicitar.

Com os melhores cumprimentos.

O Vogal do Conselho de Administração,


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Matthews DE, Farewell VT: *Using and Understanding Medical Statistics*, ed 4, revised. Basel, Karger, 2007.

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Costa-Pinto FA, Basso AS: Neural and behavioral correlates of food allergy; in Bienenstock J (ed): *Allergy and the Nervous System*. *Chem Immunol Allergy*. Basel, Karger, 2012, vol 98, pp 222–239.

(e) Websites:

Karger Publishers: *Transforming Vesalius: The 16th-Century Scientific Revolution Brought to Life for the 21st Century*. Basel, Karger, 2013.
<http://www.vesaliusfabrica.com/en/new-fabrica.html>.

(f) Websites with access date:

World Health Organization: Leprosy elimination project: status report. 2003.
<http://www.who.int/lep/Reports/s20042.pdf> (accessed May 15, 2005). Reference Management Software: The use of EndNote is recommended to facilitate formatting of citations and reference lists. The journal output style can be downloaded from <http://endnote.com/downloads/styles>.



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